# GLYCYRRHIZIN-INDUCED INHIBITION OF THE PITUITARY-ADRENAL STRESS RESPONSE*, ‡, §

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Since the desoxycorticosterone-mimetic action of glycyrrhizin has been reported, clinicians have been interested in its pharmacodynamics and possible therapeutic value. The minerosteroid-like activity of crude licorice extract was first observed in normal individuals (1, 2). Subsequently, both the active principle, glycyrrhizinic acid (3) and the crude extract have been shown capable of replacing desoxycorticosterone in treatment of patients with Addison's disease (3–8) or with total adrenalectomy (9). Glycyrrhizin-induced retention of sodium and water has been demonstrated in both intact (10) and adrenalectomized (10, 11) rats.

The action of glycyrrhizin further resembles that of desoxycorticosterone in its inhibitory effect on the pituitary-adrenal system (10, 12). Animals treated with glycyrrhizin develop adrenal cortical atrophy (12) and show less than normal reduction of adrenal ascorbic acid in response to histamine (10). In the present investigation two additional indices of pituitary-adrenal function, namely resistance to cold stress and capacity to mobilize glucose during fasting, were studied in normal and glycyrrhizin-treated animals.

## *Methods*

*Resistance of Mice to Prolonged Cold Stress.*—The survival rate as a measure of resistance to prolonged stress was determined in glycyrrhizin-treated and untreated mice. Male mice, 8 to 10 gm., (10 untreated and 10 treated) were individually housed, and exposed for 8 hours to a temperature of 5°C. Glycyrrhizin-treated mice had received 0.4 per cent ammoniated glycyrrhizin in place of drinking water for 4 days prior to stress.

*Glucose Mobilization of Rats Subjected to 48 Hours of Fasting.*—Fasting of rats causes an initial hypoglycemia followed by a pituitary-adrenal response with mobilization of glucose (13). The concentration of glucose in blood after 48 hours of fasting was observed in 5 treated and 5 untreated male rats (145 to 150 gm.), the glycyrrhizin-treated rats having received 0.4 per cent ammoniated glycyrrhizin in place of drinking water for 1 week prior to the test.

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* Ammoniated glycyrrhizin granules supplied by S. B. Penick and Co., New York.

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Blood glucose levels were determined on tail vein blood at 0, 24, and 48 hours. The capacity to mobilize glucose was judged from the relative values at 24 and 48 hours.

## RESULTS

*Resistance to Prolonged Cold Stress.*—Glycyrrhizin-treated mice died more rapidly than untreated mice during exposure to cold stress for 8 hours (Fig. 1). The median survival times for untreated and treated mice were 6.5 and

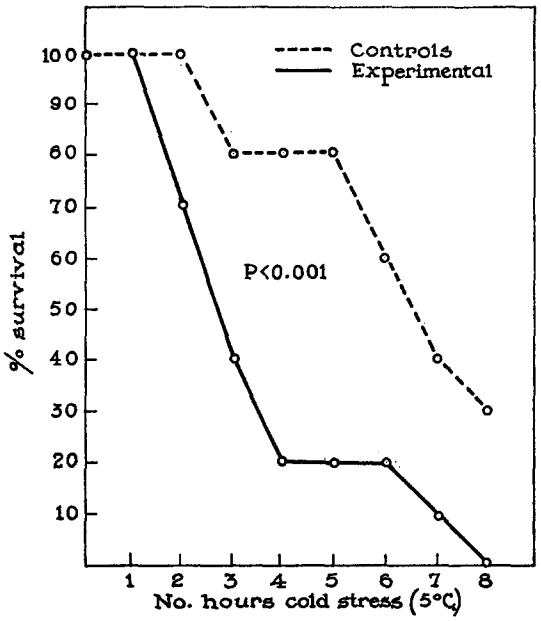


FIG. 1. Survival rate of glycyrrhizin-pretreated male mice (intact) 8 to 10 gm., subjected to cold stress (5°C.) compared with untreated controls. Experimental animals received ammoniated glycyrrhizin (0.4 per cent) *ad libitum* for a period of 4 days prior to stress. Ten animals in each group, individually housed and stressed for 8 hours. Median survival times: controls 6.5 ± 0.5 hours; experimental 2.6 ± 0.6 hours (60 per cent less than controls $P < 0.001$).

2.6 hours respectively (Fig. 1). The resistance of mice treated with glycyrrhizin was 60 per cent less ($P < 0.001$) than that of the untreated controls (Fig. 1).

*Glucose Mobilization after 48 Hours of Fasting.*—Glycyrrhizin decreased the ability of rats to mobilize glucose (Fig. 2). After 24 hours of fasting both groups exhibited the expected degree of hypoglycemia (Fig. 2). After 48 hours, untreated rats had mobilized sufficient glucose to bring the blood glucose level up to a value which was not significantly different from the control (Fig. 2). In contrast, the 48 hour blood glucose of glycyrrhizin-treated rats was significantly ($P < 0.01$) depressed.

## DISCUSSION

Cold and fasting presumably increase adrenocortical activity through release of ACTH,[1] the degree of adrenocortical activity depending upon the quantity of hormone released from the pituitary and the responsiveness of the adrenal cortex (14). In the present study, the normal animals responded

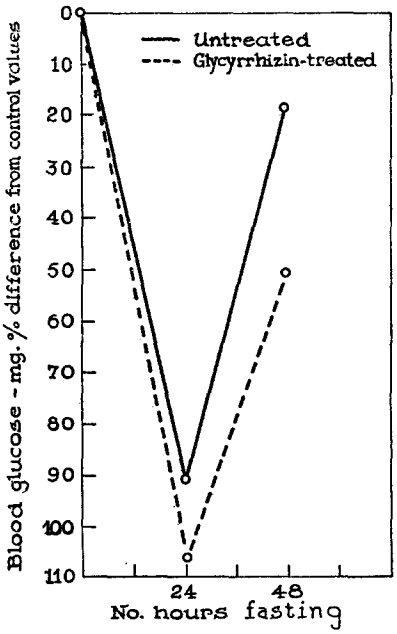


FIG. 2. Glucose mobilization response of glycyrrhizin treated and untreated intact male rats subjected to 48 hours of fasting stress. Experimental animals received ammoniated glycyrrhizin (0.4 per cent) *ad libitum* for 1 week prior to stress. 5 animals in each group. Blood glucose determined on tail vein blood at 0, 24, and 48 hours of fasting. Analysis of variance:—

1. 24 hours of fasting (hypoglycemia): (*a*) difference from control; untreated P 0.01, treated $P < 0.01$. (*b*) difference between groups; not significant.

2. 48 hours of fasting (glucose mobilization): (*a*) difference from control; untreated not significant, treated $P < 0.01$; (*b*) difference between groups; treated 22.8 per cent of the response of untreated (P 0.05).

to these stresses with increased production of corticoid, as evidenced by their resistance to the stresses and by the mobilization of glucose. Those treated with glycyrrhizin had a higher mortality and a diminished mobilization of glucose. These observations, coupled with the decrease in adrenal ascorbic acid response (10) and the atrophy of the adrenal cortex (12) observed in glycyrrhizin-treated animals, strongly suggest that glycyrrhizin depresses the output of ACTH.

[1] Adrenal corticotrophic hormone.

Desoxycorticosterone exerts a similar inhibitory effect on the pituitary-adrenal system through depression of ACTH release (15). Like glycyrrhizin it causes adrenal cortical atrophy (15, 16), diminished adrenal ascorbic acid response (15), diminished glucose mobilization and impaired resistance (16). Although the mechanism of action of glycyrrhizin is as yet unknown, its actions strongly resemble desoxycorticosterone in both its effect on the pituitary-adrenal system as well as its effect on electrolyte metabolism (1–11).

SUMMARY

Glycyrrhizin decreased the resistance of intact male mice to prolonged exposure to cold (8 hours at 5°C.) and it decreased the ability of intact male rats to mobilize glucose when subjected to 48 hours of fasting. It is suggested that glycyrrhizin, like desoxycorticosterone, depresses the output of ACTH.

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